REMARKS

Applicants have amended Claims 3, 4, 6-14, and 22-24. The amendments add no new matter to the claims. Applicants have cancelled Claim 1 and added new claims 25-27.

Request for Withdrawal of Finality of Office Action

The Examiner has made the Office Action dated 9/17/2004 a Final Office Action based on MPEP 706.07(a), stating that the Applicant's addition of new Claim 23 necessitated the new grounds of rejection. However, the Examiner has rejected not only new Claim 23, but also pending Claims 1, 3-4, 6 and 11-12, as being anticipated by Lutfalla et al.. The MPEP 706.07(a) states "a second action....will not be made final if it includes a rejection, on newly cited art,....of any claim not amended by applicant or patent owner in spite of the fact that other claims may have been amended to require newly cited art. The Examiner states that it is new claim 23 which prompted the new rejection. The rejection of Claims 1, 3-4, 6 or 11-12 could have been made in a previous Office Action, but was not. Therefore, rejection of these claims was not necessitated by the amendment made by the Applicants in their response filed June 14, 2004.

MPEP 706.07(a) further states that "a second action...should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed. Applicants contend that the limitations added in Claim 23 would have been reasonably expected, given the Examples present in the Specification.

Applicants believe that in light of the arguments presented above, the finality of the Office action dated 9/17/2004 should be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has upheld the rejection of Claims 1, 3-4 and 6-14 under 35 U.S.C. §112, first paragraph, for not being enabling for the invention as claimed.

Applicants have cancelled Claim 1 and replaced it with new claim 25. Support for this claim can be found in the Specification, in Examples 4-6, where it is shown that (1) anti-proliferative effects of type I IFN are increased in cells transfected with IFNAR2c as compared with untransfected parental cell lines *in vitro* and (2) that this effect can also be seen in an *in vivo* model, in which lung tumors derived from LOX human melanoma cells (parental or IFNAR2c-transfected) are treated with systemic Betaseron™ (see Example 6 and Figure 10).

Further support can be found in a recent publication by the inventors (Wagner et al. *Int. J. Cancer* (2004) 111:32-42), in which the results of the experiment described in the Specification on page 20, lines 18-25, are shown (see Table III, page 40 of Wagner et al.). In this case, a human xenograft model is used to examine the sensitivity of MDA231 cells, both parental and IFNAR2-c-transfected, in an *in vivo* mouse xenograft model. The results clearly indicate that cells transfected with the IFNAR2-c gene show increased sensitivity to treatment with a Type I IFN (Betaseron™), resulting in a decrease in tumor burden.

Applicants have described the utility of increasing IFNAR2-c receptors in the treatment of diseases characterized by unwanted cell proliferation (see Specification, pg 7, line 22 to pg 8, line 1). In this section of the Specification, several methods are described for delivery of the IFNAR2-c gene to cells *in vivo*, e.g. the use of viral vectors such as adenoviral or retroviral vectors. Support for this approach can be found in a publication by Qin et al. (*Proc. Natl. Acad. Sci.* 95:14411-14416, 1998), which describes the use of gene therapy in which IFNβ was delivered to tumors, resulting in tumor regression. In the Specification (page 8, lines 9-11), it is contemplated that gene therapy can be used to deliver both the IFNAR2c polypeptide and the IFN ligand. Qin et al. Demonsstrate the feasibility of this approach.

Applicants have shown the responsiveness of tumors to IFN therapy in *in vivo* models, where the tumors are derived from IFNAR2-c transfected cells. The Qin et al. article demonstrates that gene therapy using IFNβ results in tumor regression. Applicants contend that one skilled in the art would be enabled to develop a gene therapy approach in which these two elements are combined.

Applicants believe that in light of the amendments to the claims and the arguments presented above, the rejection of Claims 1-4 and 6-14 under Section 112, first paragraph, has been overcome and respectfully request its withdrawal.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1, 3-4, 6-14 and new claims 22-24 under 35 U.S.C. §112, second paragraph, for being indefinite. The Examiner has indicated that the phrase "the anti-growth effects" in claim 1 and its dependent claims is unclear as to which anti-growth effects are being claimed. Applicants have cancelled claim 1 and replaced it with new claim 25, which contains the language "wherein anti-growth effects of a type I interferon are potentiated". It is clear from the Specification (page 2, lines 15-21) that Applicants are referring to any anti- growth effects on a cell which result from treatment with a type I interferon. As demonstrated in Table I, on page 16 of the Specification, Applicants employed a number of assays; i.e. apoptosis, cell death, anti-proliferation, to measure various anti-growth effects.

The Examiner has indicated that new claims 22 and 24 are indefinite because the phrase "further comprising introducing exogenous polynucleotide encoding the IFNAR2c polypeptide into cells in culture to form said modified cell" does not make clear what the relationship or connection between cells in culture and a target cell population is. Applicants have amended claims 22 and 24 to indicate that the cells into which the IFNAR2c polypeptide is being introduced are "cells of said target cell population", thus clarifying the connection between the cells in culture and the target cell population. Claims 22 and 24 have been amended to change their dependency from cancelled claim 1 to new claim 25.

Applicants believe that with the introduction of new claim 25 and the amendments to claims 22 and 24, the Examiner's rejections have been addressed and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §102 (b)

The Examiner has maintained his rejection of Claims 1-4, 6 and 12-13 under

35 U.S.C. §102 (b) as being anticipated by Domanski et al. (*J. Biol. Chem.* 273:3144-3147, 1998).

The Domanski et al. reference describes experiments in which L-929 mouse cells have been transfected with and are co-expressing a wild-type human IFNα receptor chain and a series of mutant human IFNβ receptor chains, which have been truncated at varying amino acid positions on the β chain sequence. Domanski et al. show that these transfected cells demonstrate an anti-viral response in the presence of IFNβ. The Examiner argues that because these cells demonstrate the anti-viral effects of IFNβ, other effects seen in cells in response to treatment with type I IFNs are "inherent", and therefore the anti-growth effects claimed by the Applicant would be anticipated by this reference. The Examiner states "there is no evidence suggesting or indicating that the method taught by Domanski et al. having the same method steps and the same materials (a cell and IFN concentrations within a therapeutically effective amount) would not result in antiproliferative effects for the transfected cells".

Applicants provide as evidence another reference, enclosed herewith, from the same group of investigators (Platanias et al., *J. Biol. Chem.* 273:5577-5581, 1998). In this paper, the authors examined the antiproliferative response to IFNβ of those same transfected L-929 murine cells. The data demonstrates that while human IFNα2 and IFNβ produce an antiviral response in these cells (as described in the earlier Domanski reference), **the cells do not respond to the antiproliferative effects of human type I IFNs** (see abstract).

Applicants believe that in light of this reference, which presents evidence that the method taught by Domanski et al. does not result in antiproliferative effects, the rejection of Claims 1-4, 6 and 12-13 should be withdrawn and respectfully request their withdrawal by the Examiner.

Rejection under 35 U.S.C. §102 (b)

The Examiner has rejected Claims 1, 3-4, 6, 12-13 and 23 under 35 U.S.C. §102 (b) as being anticipated by Lutfalla et al. (*EMBO J.* 14:5100-5108, 1995).

Lutfalla et al. disclose experiments involving a mutant cell line, U5A, which are completely defective in IFN αβ binding. When these cells were stably transfected with a vector expressing human IFNAR2-2 (equivalent to IFNAR2-c), the transfected U5A cells exhibited an anti-viral response when exposed to IFN αβ. The Examiner states that Lutfalla et al. anticipates the instant claims, arguing that an anti-growth response in these cells following exposure to IFN would be inherent.

Lutfilla et al. demonstrate transfection of a human cells which are totally lacking in responsivness to IFN αβ. Initial experiments determined that the lack of response could not be complemented by transfection with the IFNAR1 subunit and subsequent studies then showed that response was restored by transfection with the IFNAR2 subunit. As the response to the IFN ligand results from interaction of the ligand with a complex of the IFNAR1 and IFNAR2 polyeptides, the availability of either polypeptide could prove limiting in forming the complex necessary to result in a cellular response (either anti-viral or anti-growth) to IFN αβ. In the example presented by Lutfalla et al., in which IFNAR2-c is absent, one of skill in the art would consider it likely that addition of a missing component would restore responsiveness. In the instant invention, however, cells which normally do respond to IFN (i.e. HT1080 and MDA231 cells) demonstrated increased responsiveness to IFN following transfection over the parental untransfected cell line. Such results could not be anticipated, since it is possible that something other than the cellular level of IFNAR2-c polypeptide could be a limiting factor in the cellular response to IFN αβ.

Furthermore, Applicants have cancelled Claim 1 and replaced it with new claim 25, to further clarify the Applicants' invention. While the cited reference Lutfilla et al. demonstrates that transfection of mutant human cells with a vector expressing the IFNAR2-c polypeptide can restore sensitivity to human type I IFN in cells lacking this receptor, Lutfalla et al. **does not contain any disclosure or suggestion** that increasing the number of IFNAR2-c receptors on the surface of cells would provide a method of inhibiting cell proliferation or for treating diseases characterized by a proliferative cell condition.

Applicants believe that in light of new Claim 25 and the arguments presented above, Lufilla et al. does not anticipate the claims and therefore respectfully request withdrawal of this rejection.

Conclusion:

Applicants respectfully submit that with the submission of amended Claims 3, 6-14, and 22-24 and new claims 25-27 and the arguments present above, the application is now in condition for allowance. Such action is solicited at an early date.

Respectfully submitted,

Wendy L. Washtien

Wendy L. Washtien, Ph.D.
Agent for Applicant
Reg. No. 36,301

Berlex Biosciences
2600 Hilltop Drive
Richmond, CA 94806
Telephone: (510) 262-5411
Fax: (510) 262-7095
Date: December 22, 2004